The 2009 H1N1 Pandemic Influenza Virus: What Next?

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ABSTRACT History suggests that the 2009 pandemic H1N1 influenza virus faces extinction unless it mutates to avoid already high global population immunity. The immune escape mechanisms potentially at its disposal include antigenic drift, antigenic shift via genetic reassortment, and intrasubtypic reassortment. Going back to the late 19th century, the evolutionary histories of past pandemic viruses are examined in an effort to better understand the nature and extent of the immune pressures faced by the 2009 pandemic virus in the immediate future. While human influenza viruses have often surprised us, available evidence leads to the hope that the current pandemic virus will continue to cause low or moderate mortality rates if it does not become extinct.

It has been one and a half years since the emergence of the 2009 novel pandemic H1N1 influenza virus (pH1N1), which caused a global pandemic in 2009-2010 (1). As we approach the 2010-2011 influenza season in the Northern Hemisphere, it is reasonable to speculate as to what role this virus will have in the upcoming influenza season in the United States. The pH1N1 virus is still circulating throughout the world, albeit at much lower levels than during the 2009-2010 influenza season (2), and it is extremely likely that infections with pH1N1 will occur in the United States during the 2010-2011 influenza season. The impact of this virus during the upcoming influenza season will depend directly on the degree of existing immunity in the population, i.e., population immunity, provided that no significant antigenic change of the virus occurs.

Population immunity against pH1N1 in 2010-2011 will comprise a combination of factors, including the immunity raised by prior exposures to cross-reacting viruses and vaccines, the extent of infection with pH1N1, and the relative proportion of the population vaccinated against the virus in 2009-2010. Potential evasive responses of a virus to population immunity include antigenic drift (sequential antigenic changes in hemagglutinin [HA] that lead to immune escape), antigenic shift (importation by reassortment of a gene encoding a different HA subtype with or without additional viral genes), and intrasubtypic reassortment (ISR; importation by reassortment of a gene encoding an antigenic variant of the same HA subtype with or without other genes [3, 4]).

Even before pH1N1 was detected in March 2009, the global population had a considerable degree of protective immunity to it. Seroprevalence data from the United States and elsewhere indicate that approximately 19% of the U.S. population had antibody titers that neutralized at dilutions of 40-fold or greater (believed to correlate with a substantial degree of protection [5]), presumably due to some combination of prior exposures to related viruses and vaccines. These exposures include infection by descendants of pH1N1's ancestral 1918 pandemic H1N1 virus (5), vaccination in the 1958-to-1967 era with human polyvalent vaccines containing both seasonal and swine H1N1 antigens (6), vaccination with a closely related 1976 swine influenza vaccine (7), and cross-immunity elicited by more-recent but less closely related seasonal viruses and vaccines (5, 7, 8). Because both higher antibody levels and higher age-specific frequencies of antibody against pH1N1 were more strongly associated with exposures to pre-1957 H1N1 viruses, protection appeared to be concentrated in persons older than ~55 years (alive during the 1918-to-1957 H1N1 era [5, 9]).

One and a half years after the appearance of pH1N1, population immunity in 2010 is substantially higher than it was prior to the emergence of the pandemic virus (Fig. 1) (5, 8–11), and this immunity is likely to rise substantially with administration of vaccines in the 2010-2011 influenza season (10, 11). In addition to the ~19% of the U.S. population of ~310 million with preexisting immunity (around 60 million persons) (http://www.census.gov/population/www/projections/summarytables.html), there are another ~62 million persons who have been immunized (20%, representing those among the conservatively estimated 72 million vaccinated persons who were not already immune) and an additional 61 million persons (20%) who were naturally infected, suggesting a current population immunity of ~59% in the United States. Given the relatively low number of infections estimated so far for persons older than 50 years (Fig. 1) and the possibility that standard measurements may underestimate immunity, there may be a higher degree of population protection than predicted.

In this regard, we do not know the extent to which preexisting cross-reactive antibodies can prevent infection or disease. It is noteworthy that in past pandemics (e.g., the 1957-1958 pandemic), significant numbers of persons with probable prior exposures but without detectable cross-reactive antibodies seem nevertheless to have been protected (12), as were some people with low-level cross-reactive antibodies against distantly related viruses (6). If the 1976 vaccine is protective without contributing high-level neutralizing antibodies, as many as an additional 8.3% of the population might be partially or fully protected by it, even >30 years later (7). Moreover, immunity to neuraminidase (NA) and conserved T cell epitopes (13), as well as anamnestic (boosting) and "original antigenic sin" immune responses (14, 15), might provide additional protection from infection or severe disease. Clearly, a large percentage of the U.S. population must already be immune to pH1N1, reducing opportunities for explosive pandemic spread in the future.

In the face of such high levels of immunity so soon after emergence of the pandemic virus, what options for continued circulation does pH1N1 have? While pandemic and seasonal influenza viruses have frequently surprised us, we should at least look at their past behavior for guidance. In the past 120 years, pandemic influenza vi-

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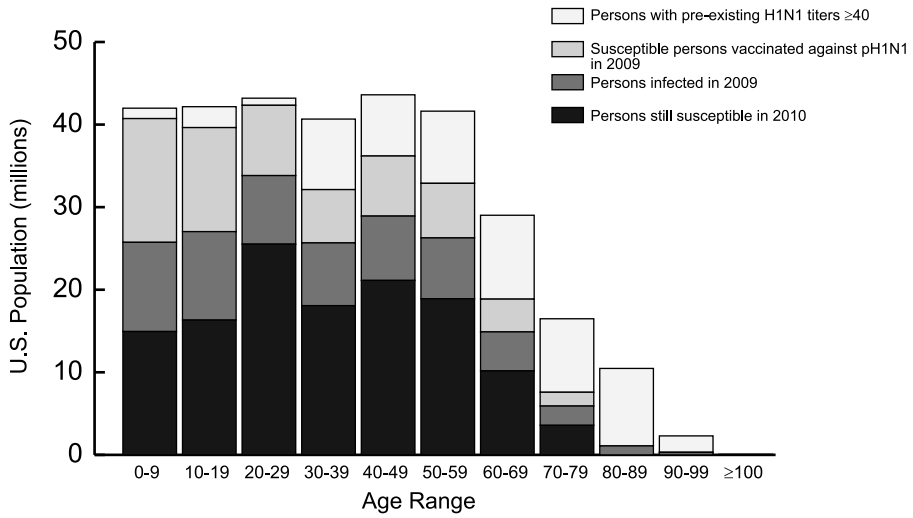

FIG 1 Estimation of age-specific population immunity to pH1N1 in the United States in 2010, calculated using 2009 seroprevalence data based on neutralization titers of ≥40 (5), on 2009-2010 immunization data (11), and on 2009 infection data (9). The data, assembled for illustrative purposes, are based on estimates from small nonrandom samples and on preliminary public health figures. Calculations assume that a proportional segment of the vaccinated population was already naturally immune to pH1N1 and that infections occurred only in persons who were both nonimmune in early 2009 and not vaccinated before being infected.

ruses have established continuing circulation by one or more of the following four mechanisms: (i) explosive recurrences and "waves" (16) in (apparently) completely naïve (e.g., 1889) or partially immune (e.g., 1918) populations, (ii) generation of novel pandemic viruses by antigenic shift (e.g., descendants of the 1918 H1N1 virus in the pandemics of 1957 and 1968 [17]), (iii) seasonal viral evolution by intrasubtypic reassortment (ISR; e.g., 1918 viral descendants in 1947 and 1951 [18], a 1957 H2N2 descendant in 1967 [19], and 1968 H3N2 descendants in 1997 and 2003 [3, 4]), and (iv) continuing long-term seasonal circulation by antigenic drift (20).

Regarding the first of these possibilities, i.e., early explosive recurrences, it is noteworthy that population immunity to pH1N1 has probably already surpassed what past pandemic viruses have normally achieved in their first year (12, 21, 22). Moreover, in the last six pandemics (going back 163 years), explosive recurrences generally have not been observed or occurred at most on only one occasion within the first few years. The chief exceptions were the 1889 pandemic, when an as-yet-unidentified virus apparently struck a completely susceptible population and had one to four mostly seasonal recurrences, and the 1918 pandemic, in which one to three "waves" of mortality were seen in different locations, possibly because of seasonal timing (16). Explosive recurrences of pH1N1 may therefore be unlikely because of high and increasing population immunity.

The second possibility is an additional antigenic shift, as occurred in 1957 and 1968, after antigenic drift over lengthy time periods (39 and 11 years, respectively). Because the U.S. population in 2010 already has moderate or high immunity to the two other HA subtypes identified in human-adapted influenza viruses, H2 (in persons born before 1968, who constitute about 56% of the U.S. population [172.4 million persons]) and H3 (in persons of all ages), the population impact of an H2 or H3 shift would probably be blunted. A shift to a novel HA, if it is even possible (17), given the long-held hypothesis that only a limited number of HAs can be incorporated into human-adapted viruses and that these HAs "recycle" when exposed birth cohorts die off (23), would have unpredictable consequences. However, it is noteworthy that successively decreasing severity has been associated with each antigenic shift since 1918 for reasons that are not yet fully understood (24–32) (http://www.cdc.gov/mmwr/index.html). pH1N1 could potentially reassort with seasonal H3N2 or H1N1 viruses. Moreover, reassortment with cocirculating seasonal H1N1 could conceivably result in the creation of an oseltamivir-resistant pH1N1 lineage (33), which would complicate treatment and prophylaxis of at-risk patients. Likewise, infection of swine with pH1N1 and additional reassortment with other currently circulating swine influenza viruses have already been identified (34), potentially leading to novel viruses that could infect humans.

Similarly, ISR, which can be thought of as a "minor shift," cannot be ruled out as a possible means of pH1N1 survival. Had this type of genetic change occurred in the previrology era, it might not have left a recognizable epidemiological signature, as some presumed antigenic shifts did. However, it seems likely that in the past 92 years, ISR, as a mechanism for generating widely circulating viruses with either antigenically variant HAs or other gene constellations that confer enhanced viral fitness, has been selected for on only five occasions, and only after relatively long periods of antigenic drift (28, 33, 10, 29, and 35 years [1]). Curiously, ISRs have clustered at 4- to 6-year intervals for both H1N1 and H3N2 viruses, in 1947 to 1951 and 1997 to 2003, respectively; this is an unexplained and possibly nonrandom occurrence. As with known past antigenic shifts and ISRs, high population immunity to circulating H1N1 viruses and vaccines would very likely afford partial protection if pH1N1 ISR occurred.

Regarding the final possible known mechanism, antigenic drift, it is worth noting that the ability to drift perpetually to escape evolving population immunity may not be a property shared to the same degree by all human influenza viruses (Fig. 2) (8, 24–32, 35) (http://www.cdc.gov/mmwr/index.html). The H3N2 virus has been drifting significantly more rapidly than either of its H1N1 and H2N2 ancestors, in the process causing recurring mortality peaks (8, 24–32, 35) (http://www.cdc.gov/mmwr/index.html). In fact, H3N2 viruses have caused localized outbreaks in June-July 2010 in the United States (36). Both the 1918 H1N1 and the 1957 H2N2 virus lineages drifted as seasonal influenza viruses to a point of low incidence and mortality

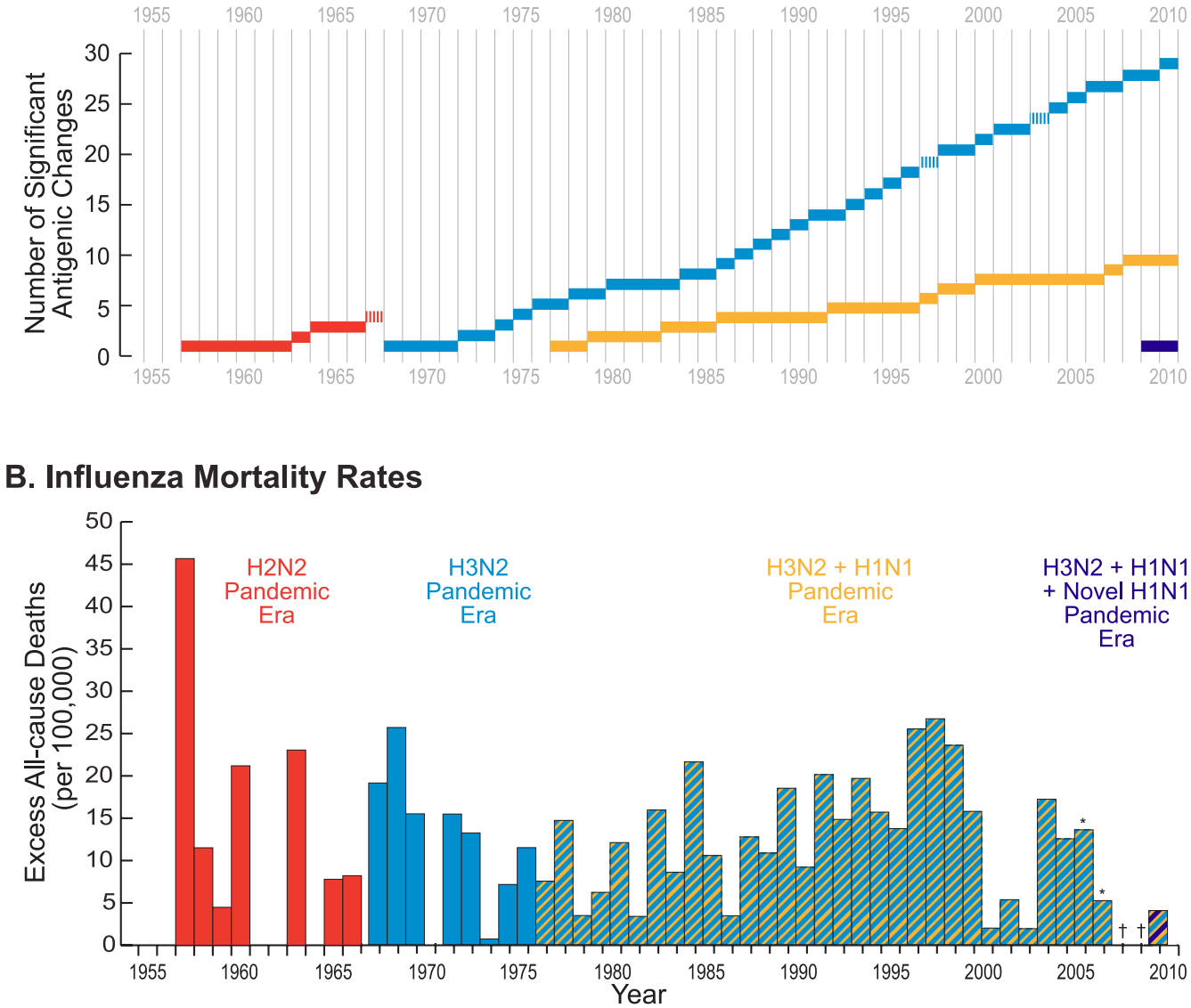

FIG 2 Drift/ISR history of four pandemic influenza viruses (A) and annual rates of all-cause excess mortality per 100,000 persons (B) in the United States from 1957 to 2010 (24–32, 35) (http://www.cdc.gov/mmwr/index.html). On the upper panel, drift/ISR are indicated by significant antigenic change detected by virologic and serologic means (1957 to 1967) (24) or by vaccine composition data from the World Health Organization (8) and the Centers for Disease Control and Prevention (http://www.cdc.gov/mmwr/index.html). Data in panel A are based on modifications of data from the World Health Organization (8). Red, H2N2; blue, H3N2; yellow, seasonal H1N1; purple, pH1N1. ISRs in panel A are indicated by vertical hatching. The data suggest that the 1968 H3N2 virus has been evolving rapidly (2 ISR and 22 drift changes of major significance in 43 years; mean, 0.56 changes per year), while seasonal H1N1 (9 drift changes in 34 years; mean, 0.27 changes per year) and H2N2 (1 ISR and 2 drift changes in 11 years; mean, 0.27 changes per year) have evolved significantly more slowly. Because of the unavailability of all-cause excess mortality data for 2005-2006 and 2006-2007, estimates of annual influenza-associated deaths with underlying respiratory and circulatory causes are displayed for the years marked with an asterisk (35). For discussion of the various types of estimates of excess influenza mortality, see Thompson et al. (31). †, data unavailable.

and then disappeared entirely. Furthermore, it is not known at this point how pH1N1 evolution will affect the circulation of H3N2 and H1N1 viruses and vice versa.

We have little information concerning the determinants of the capacity for antigenic drift. We do not know whether this capacity is inherent in all influenza viruses or a chance property of the founding viral HA such as mutational repertoire or the ability to add HA glycosylation to achieve antigenic masking. Nor is it known how likely reassortment with antigenic shift is for viruses inherently unable, or no longer able, to escape immunity via successful antigenic drift. With respect to H1N1 viruses, we do not understand how and why a slowly drifting and relatively avirulent virus like seasonal H1N1 reemerged in 1977 in a partially immune population from which it had disappeared entirely with the emergence of the 1957 H2N2 virus 20 years earlier (Fig. 2) (17). We do not understand how, after initially infecting only individuals under 20 years of age, it continued to circulate with minimal drift up to the present (33 years) in a population with high/growing im-

munity. Related questions include how and why high population immunity has been associated with rapid seasonal H3N2 drift, but with only slow seasonal H1N1 drift, and why such conditions have not resulted in H1N1 extinction. Other factors to be addressed include the potential impact of various global infection and vaccination experiences on the evolution of pH1N1. In this regard, most of the global population has far lower rates of pH1N1 and seasonal influenza vaccination and influenza virus circulation patterns differ globally (4). Clearly, profound mysteries about human influenza viral evolution remain. These issues are of practical importance because viruses with reduced ability to drift, or even the establishment of new pandemic viruses, might potentially be eliminated by the development of herd immunity following continued high levels of vaccination (37).

In summary, history suggests that pH1N1 likely faces extinction unless it mutates, either by mechanisms (such as antigenic shift or ISR) that have never been documented to occur in early pandemic years or by successful antigenic drift, whether slow (as with seasonal H1N1) or aggressive (as with H3N2). Apart from population immunity, the factors driving pH1N1 evolution, such as the inherent evolutionary properties of the founding viral HA, NA, and other viral genes (for a review, see reference 38) as well as competition with seasonal H1N1, are poorly understood.

Past history and current understanding suggest cautious optimism that pH1N1 will eventually adapt to stable circulation via genetic changes resulting in continuing moderate or low mortality rates or possibly even disappear entirely. Nevertheless, it is noteworthy that other postpandemic viruses have continued to cause various rates of excess mortality among younger persons for years after pandemic appearance (39). The first year of pH1N1 circulation has given us important information that allows us to plan for the immediate future. Until such time as a major antigenic change occurs, the population over ~50 years old should remain substantially protected with standard annual influenza vaccination and optimal existing public health and medical practice. The bulk of the still-susceptible population proportionally spans the under-50 age group (Fig. 1). Thus, infants older than 6 months of age, children, teenagers, and young and middle-aged adults (the population disproportionately affected by the pandemic in 2009) will be aggressively targeted for influenza vaccination (40) for the sake of individual protection as well as for contribution to the development of herd immunity and decreased spread to susceptible individuals (37).

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